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Do antiepileptic drugs cause premature atherosclerosis by disturbing lipid metabolism?

Evaluation of premature atherosclerosis in patients with epilepsy

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Abstract

Aim: The aim of this study was to evaluate susceptibility to atherosclerosis in epileptic patients on carbamazepine and valproic acid monotherapy with lipid profile, lipoprotein (a) (lp(a)), oxidized low-density lipoprotein (LDL), adiponectin, and carotid artery intima-media thickness measurements.

Material and Methods: Of the 108 patients with epilepsy included in the study, 64 (36 female, 28 male) were receiving valproic acid monotherapy and 44 (25 female, 19 male) were receiving carbamazepine monotherapy. The control group comprised 48 (30 female, 18 male) healthy participants. Liver and kidney function tests, cholesterol, triglycerides, LDL, high-density lipoprotein (HDL), lp(a), oxidized LDL, adiponectin, and common carotid (CCA) and internal carotid artery (ICA) intima-media thickness (IMT) were investigated in both the patient and control groups.

Results: Mean age was 32.34±12.41 years in the valproic acid group, 32.70±11.64 years in the carbamazepine group, and 35.81± 11.76 years in the control group. Liver and kidney function test results were normal in all groups. Cholesterol levels were lower in the valproic acid group than the other groups. HDL levels were higher in the carbamazepine group than other groups. Adiponectin levels were lower in the valproic acid group. In all groups, cholesterol and LDL levels were higher in individuals older than 50 years old. When the patients were evaluated according to the duration of drug use, cholesterol and LDL levels were higher in patients who had used drugs for more than 5 years in the valproic acid group. There were no differences between the groups for triglyceride, oxidized LDL, or lp(a) levels or CCA and ICA IMT.

Discussion: There are conflicting results in the literature regarding epilepsy and atherosclerosis associated with antiepileptic drug usage. In this study, no evidence was found of an increasing risk of arteriosclerosis associated with antiepileptic drugs by measuring lipids, lipoprotein, oxidized LDL, adiponectin levels, and CCA and ICA IMT. However, it is important to monitor lipid levels in the follow-up of patients with epilepsy, especially for patients requiring long-term antiepileptic therapy and also older patients.

Keywords

Epilepsy, Antiepileptic Drug, Atherosclerosis, Lipoprotein, Carotid Intima-Media Thickness

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Introduction

Atherosclerosis (AS) is the common pathological basis of several cardiocerebral diseases that may cause mortality and morbidity [1]. Epilepsy is a common neurological disorder that affects people of all ages, races, social classes, and geographical regions [2]. Epilepsy requires long-term or sometimes lifelong therapy. Several recent studies have been conducted to determine whether antiepileptic drugs (AEDs) increase the risk of atherosclerosis because of metabolic changes, in addition to their known side effects, but the results of these studies are conflicting [3-6]. Some of them have reported that long-term exposure to AEDs may play a pivotal role in the pathogenesis of atherosclerosis in patients with epilepsy [3, 7, 8].

Carotid intima-media thickness (IMT) is a representative measure of atherosclerosis. Evaluation of both common carotid artery (CCA) and internal carotid artery (ICA) IMT is an important marker in investigating atherosclerosis [9]. The first morphological changes of arterial walls can be visualized by B-mode ultrasonography. Assessment by carotid ultrasonography is noninvasive and useful in the risk assessment of future cerebral or cardiovascular events according to atherosclerosis [10].

The aim of this study is to evaluate susceptibility to atherosclerosis in epileptic adults on valproic acid (VPA) or carbamazepine (CBZ) monotherapy based on carotid artery IMT measurements and levels of serum lipids, lipoprotein (a) (lp(a)), oxidized low-density lipoprotein (ox-LDL), and adiponectin.

Material and Methods

Study Population

This cross-sectional and case-control study included consecutive patients admitted to an epilepsy outpatient clinic. The participants were evaluated at the University of Health Sciences İzmir Tepecik Education and Research Hospital. Patients older than 18 years with disease duration of at least 1 year were included. Presence of ischemic stroke, history of cardiac or peripheral vascular disease, diabetes mellitus, pregnancy, smoking, renal or hepatic failure, and hormone replacement therapy were exclusion criteria. Written consent was obtained from the participants. The study was conducted according to the ethical principles suggested in the Declaration of Helsinki and the study protocol was approved by the institutional review board.

We initially enrolled 124 patients with epilepsy. Of those 124 patients, 6 had diabetes mellitus, 3 had coronary artery disease, 1 was pregnant, 1 was using hormone replacement therapy, and 5 were smokers. Those individuals were excluded from the study and a total of 108 patients with epilepsy, 64 of whom received VPA monotherapy and 44 of whom received CBZ monotherapy, were included. Forty-eight healthy participants were also enrolled as a control group. Demographic data including sex and age, duration of epilepsy, type and frequency of seizures, and duration of treatment were recorded. To investigate the effect of the duration of antiepileptic therapy on IMT, lp(a), ox-LDL, adiponectin, LDL, total cholesterol (TC), and triglyceride (TG) levels, two subgroups (duration of therapy ≤5 years and >5 years) were established for the VPA and CBZ groups.

Biochemical Analysis

Following an overnight fasting period, blood samples were obtained between 8 and 10 AM before patients took their morning doses of AEDs. The blood sample to be used for lp(a), ox-LDL, and adiponectin analysis was immediately separated by centrifugation after being obtained. The supernatant was removed and stored at -85 °C until assayed.

The TC, TG, high-density lipoprotein (HDL) cholesterol, and serum concentrations of biochemical markers of liver and renal functions such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), urea, and creatinine (Cr) were measured by enzymatic colorimetric method using commercial kits (Olympus Diagnostica GmbH, Hamburg, Germany), while LDL cholesterol was estimated using the Friedewald equation (LDL = TC - (HDL + TG/5)).

Serum lp(a), ox-LDL, and adiponectin concentrations were measured by enzyme linked immunosorbent assay method using commercial kits (respectively, AssayPro, St. Charles, MO, USA; BIOMEDICA GmbH & Co. KG, Vienna, Austria; BioVendor GmbH, Heidelberg, Germany).

Intima-Media Thickness (IMT) Measurements

Examination of carotid artery IMT was performed by the same radiologist, who was blinded to the clinical and laboratory data of the participants. Ultrasonographic examinations (Nemio XG SSA; Toshiba, Tokyo, Japan) were performed with a linear band 7.5-MHz transducer. Patients were in a supine position during the examination, with the head slightly extended and rotated to the other side. The CCA IMT was measured 2 cm proximal to the bifurcation and the ICA IMT was measured 1 cm distal to the bifurcation. Measurements were made bilaterally and the far wall was evaluated. The mean of two sides for CCA and ICA was used.

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether each variable was normally distributed. Descriptive statistics including means, standard deviations, minimum values, and maximum values of the variables were computed. Subgroup analyses of parametric variables were performed using the independent samples t-test, while analyses of non-parametric variables were performed using the chi-square test. Analyses of parametric variables among these three groups were performed using one-way analysis of variance (ANOVA) followed by the post hoc Bonferroni test for multiple comparison. Finally, subgroup analyses for carotid artery IMT, age, and duration of treatment were performed using the non-parametric Mann-Whitney U test. Values of $p<0.05$ were considered statistically significant.

Results

Sixty-four patients were on VPA monotherapy (28 male, 36 female) and 44 were on CBZ monotherapy (19 male, 25 female). Forty-eight healthy controls (18 male, 30 female) were also enrolled in the study. Mean age was 32.34±12.41 years in the VPA group, 32.70±11.64 years in the CBZ group. and 35.81±11.76 in the control group. There was no statistically significant difference between the gender distributions and mean ages of the groups ($p>0.05$). The demographic

characteristics of the participants are shown in Table 1.

Liver and kidney function test results were normal in all groups. Although the values were within the normal range, GGT levels were significantly higher in the CBZ group (p<0.01).

The mean TC level was significantly lower in the VPA group than the other groups (p=0.01). HDL levels in the CBZ group were significantly higher than in the other groups (p=0.03). When all participants were evaluated by age, TC and LDL levels were significantly higher in participants older than 50 years (p=0.011 and p=0.006, respectively). There were no significant differences between the groups in terms of TG, lp(a), or ox-LDL levels (p=0.41, p=0.3, and p=0.82, respectively). The mean levels of lp(a) were 32.28 mg/dL in the control group, 30.97 mg/dL in the VPA group, and 37.34 mg/dL in the CBZ group. In all groups, the lp(a) levels were higher than 30 mg/dL, which is considered the threshold value for increased risk of early atherosclerosis. In the VPA group, adiponectin levels were significantly lower (p=0.03). The results of serum lipid profile, liver and kidney function tests, and serum lp(a), ox-LDL, and adiponectin levels of the patient groups and the control group are given in Table 2 together with statistical comparisons between these groups.

There was no statistically significant difference between groups in terms of CCA and ICA IMT (p=0.58 and p=0.42, respectively). The mean CCA and ICA IMT values for the three groups and intergroup comparisons are shown in Table 3. No significant differences were found between the CBZ subgroups in terms of IMT, lp(a), ox-LDL, adiponectin, LDL, TC, or TG levels (p>0.05). However, patients on VPA monotherapy for longer than 5 years had higher TC and LDL levels (p<0.05) (Table 4).

Table 1. Demographic and clinical characteristics of epileptic patients and controls

Demographic data	VPA (n:64)	CBZ (n:44)	Controls (n:48)
Female/Male	36/28	25/19	30/18
Age (years) mean±SD	32.34±12.42	32.7±11.64	35.81±10.76
>50 years n(%)	6 (9.4)	5 (11.4)	5 (10.4)
≤50 years n(%)	58 (90.6)	39 (88.6)	43 (89.6)
BMI kg/m² mean±SD	24.38±5.1	24.10±5.1	24.2±5.4
Duration of the therapy	8.19±6.38	11.07±8.5	-
>5 years n(%)	37 (57.8)	27 (61.4)	-
≤5 years n(%)	27 (42.2)	17 (38.6)	-
Duration of epilepsy	9.86±1.1	12.75±1.58	
Type of epilepsy N (%)			
Primary generalised	52 (81.25)	19 (43.18)	-
-JTK		19 (43.18)	-
-Myoklonic epilepsy	2 (3.12)	0 (0)	-
-Juvenile absence	5 (7.81)	0 (0)	-
Partial	12 (18.75)	25 (56.81)	-
-Simple partial epilepsy	0 (0)	2 (4.54)	-
- Complex partial epilepsy	10 (15.6)	20 (4.45)	-
- Partial epilepsy with secondary generalization	2 (3.12)	3 (6.81)	-

p for Age: 0.3; p for BMI: 0.96; p for duration of epilepsy: 0.12

Table 2. Biochemical characteristics of epileptic patients and controls

	VPA (n:64)	CBZ (n:44)	Controls (n:48)	p
TC (mg/dl)	163.43±40.16	191.11±34.19	185.50±59.09	0.01
TG (mg/dl)	119±56.71	110.27±58.56	117.53±67.89	0.41
LDL (mg/dl)	94.57±30.33	110.06±29.90	110.70±55.63	0.06
HDL (mg/dl)	49.17±11.86	57.65±14.58*	50.22±16.50	0.01
Lp(a) (mg/dl)	30.97±50.68	37.34±60.73	32.28±48.31	0.82
Ox-LDL (mg/dl)	25.18±52.38	24.17±38.39	14.06±11.73	0.3
Adiponectin (µg/ml)	13.57±4.66	15.13±3.74	16.02±4.10	0.03
Glucose	91.94±2.66	92.70±1.58	95.77±1.46	0.43
ALT(u/l)	21.53±2.43	22.57±1.76	21.15±1.50	0.94
AST(u/l)	21.69±1.34	21.30±1.04	22.88±1.44	0.70
GGT(u/l)	18.98±2.92	50.43±5.25	18.46±1.49*	<0.01
Urea(mg/dl)	30.58±1.61	25.23±1.01	30.08±2.01	0.05
Cr(mg/dl)	0.85±0.04	0.78±0.02	0.83±0.02	0.21

Data are expressed as means ± SD.

Table 3. Intima media thickness of epileptic patients and controls

	Intima-media thickness (mm)			
	VPA (n:64)	CBZ (n:44)	Controls (n:48)	p
RCC	0,64±1.46	0,63±0,13	0,61±0,15	0.71
LCC	0,66±1,17	0,63±0,14	0,61±0,15	0.49
Median CCA	0,65±0,02	0,63±0,13	0,61±0,15	0.58
RICA	0,54±0,01	0,54±0,13	0,51±0,12	0.51
LICA	0,54±0,02	0,54±0,14	0,51±0,10	0.48
Median ICA	0,54±0,01	0,54±0,13	0,51±0,10	0.42

Data are expressed as mean ± SD.

Table 4. Evaluation of Intima media thickness and Biochemical results of patients according to the duration of VPA and CBZ therapy

	VpA group (mean ±SD)		CBZ group (mean ± SD)		P1	P2
	≤5 years (n=27)	>5 years (n=37)	≤5y ears (n=17)	>5years (n=27)		
Median CCA IMT (mm)	0.648±0.127	0.64±0.15	0.64 ±0.14	0.63±0.11	0.30	0.98
Median ICA IMT (mm	0.542±0.1	0.544±0.1	0.53±0.12	0.54±0.12	0.42	0.78
OX-LDL (mg/dl)	21.30±35.54	28.02±62.20	33.76±50.46	18.13±27.80	0.70	0.72
Adiponectin (µg/ml)	14.27±4.02	13.06±5.06	14.77±3.45	15.35±3.95	0.87	0.06
Lp(a)(mg/dl)	31.98±53.86	30.23±48.97	43.08±73.18	33.72±52.62	0.19	0.11
LDL (mg/dl)	84.70[a]±25.27	101.78[a] ±31.97	105.5±31.84	112.92±28.86	0.02	0.06
TC (mg/dl)	148.35[b]±37.65	174.43[b]±38.77	188.00±34.66	193.07±34.40	0.001	0.03
TG (mg/dl)	116.92±61.22	120.75±53.99	133.82±70.26	95.44±45.19	0.49	0.053

Data are expressed as mean ± SD P1: VpA vs CBZ, theraphy duration ≤5 years, p2: VpA vs CBZ, theraphy duration >5 years. p[a]=0.025; p[b]=0.009 comparison the LDL (≤5, >5) and TC (≤5, >5) of the valproic acid group.

Discussion

Atherosclerosis is a disease of large and medium-sized arteries and is characterized by endothelial dysfunction, vascular inflammation, and changes in IMT [11]. Many recent studies have examined whether AEDs increase the risk of atherosclerosis because of metabolic changes, in addition to their known side effects, but the results of these studies are contradictory [3-5]. There are few reports about the effect of AED treatment on serum lipid profile and lipoproteins in the adult population [3-6, 12-14]. Elevated levels of serum TC, LDL [5, 6, 12, 14], and HDL were reported in pediatric patients receiving CBZ monotherapy [5, 6, 12]. In a prospective study, Verroti et al. reported that alterations in serum lipids and lipoproteins were transient [5]. Most studies in the literature reported alterations in serum lipids and lipoproteins with CBZ therapy, but Hamed et al. and Sözüer et al. did not demonstrate significant alterations in serum levels of TC, LDL, or TG in CBZ, VPA, polytherapy, or untreated groups [3, 14]. However, HDL levels were significantly lower in these groups when compared with a control group [3]. Several studies showed decreased TC [6, 12, 15], LDL [12, 15], and HDL [3, 12] levels during VPA treatment. Conversely, some studies reported similar values between the VPA group and control group for TG [3, 5, 13, 14], HDL [5, 6, 13, 14], LDL [3, 5, 13, 14], and TC [3, 5, 12-14] levels.

In this study, TC levels were significantly lower in the VPA group than the CBZ and control groups. HDL levels in the CBZ group were significantly higher than those in the other groups. There was no significant difference in TG levels between groups. These results indicate that other features such as genetics, dietary habits, or lifestyle factors might have more contributive effects on the lipid profile than AEDs.

In the literature, lp(a) has been identified as an independent risk factor for vascular disease and subjects with lp(a) values above 30 mg/dL have an increased risk of developing early atherosclerotic disease [16]. While lp(a) levels are mainly under genetic control and are less affected than other lipoproteins by age, sex, weight, and diet, there are a few exogenous factors, such as physical exercise, estrogen therapy, and end-stage renal failure, that affect lp(a) serum concentrations [17]. Data regarding AEDs and their effects on lp(a) levels are controversial and most previous studies were performed among pediatric populations. Voudris et al. reported elevated lp(a) levels in pediatric patients [18], whereas Verroti et al. showed no significant difference between the control group and pediatric epileptic patients receiving long-term CBZ or VPA [12]. In another study, elevated lp(a) levels were not statistically significant [4]. On the other hand, an increase in serum lp(a) concentrations was reported by Schwaninger et al. in adult epileptics receiving AED therapy. However, for half of those patients, a combination of different AEDs had been administered [19].

Several possible mechanisms have been proposed to explain the increase in lp(a) levels, such as the effect of renal functions on the catabolism of lp(a), the enzyme-inducing characteristics of CBZ, and AED-induced alterations in the synthesis of lp(a) [19]. There was no significant difference in levels of lp(a) between the VPA, CBZ, and control groups in our study. However, lp(a) levels in all three groups were higher than 30 mg/dL. There was no liver or renal dysfunction that affected the synthesis or metabolism of lp(a) in any of these groups. However, LDL levels were significantly lower in the VPA group than in other groups. We suggest that receiving AEDs did not affect the lp(a) levels and high levels exceeding the threshold value in all groups can only be explained by genetic predisposition.

Ox-LDL plays a role in the pathogenesis of atherosclerosis and can be a predictor for atherosclerosis in the absence of conventional risk factors such as hypertension, smoking, diabetes mellitus, and dyslipidemia [20]. It is widely accepted that oxidative modification of LDL is involved in the development of atherosclerotic lesions through the formulation of macrophage-derived foam cells and/or through pro-inflammatory effects on vascular cells [21]. This is the first step in the formulation of atherosclerotic plaque. There are few studies about the effect of AED treatment on ox-LDL [3, 22, 23]. It was reported that ox-LDL is associated with subclinical atherosclerosis [24]. Hamed et al. demonstrated unbalanced oxidative stress/antioxidant disequilibrium in both treated and untreated epileptic patients. Their study also identified reduced HDL and elevated ox-LDL levels [3]. On the other hand, Yıldız et al. investigated the effect of VPA, CBZ, and VPA-CBZ combination therapy on LDL oxidation, paraoxonase activity, thyroid hormones, and arterial distensibility (by carotid-femoral pulse wave velocity) in epileptic children; similar levels of ox-LDL and paraoxonase activity were reported in epileptic patients and control subjects. They showed increased carotid-femoral pulse wave velocity in epileptic children using CBZ and VPA. In addition, a correlation was found between pulse wave velocity, VPA, and thyroid-stimulating hormone levels [23]. In this study, there was no significant difference in terms of ox-LDL levels between the VPA, CBZ, and control groups. Although oxidant/antioxidant parameters were not evaluated in this study, due to the absence of elevated LDL levels and decreased HDL levels, we would not expect to find a difference in ox-LDL levels.

Adipose tissue is generally considered an endocrine organ, which releases various factors into the circulation system. Adiponectin is one of the adipocytokines and plays a protective role against diabetes and atherosclerosis. Research has shown that hypoadiponectinemia is associated with obesity, insulin resistance, cardiovascular disease, dyslipidemia, hypertension, and metabolic syndrome [25]. In addition, adiponectin has antiatherogenic properties, as shown by its capacity to inhibit monocyte adhesion to endothelial cells and macrophage-to-foam cell transformation [26]. There are a limited number of studies investigating the association between alteration of adiponectin levels and AED usage. Greco et al. reported that epileptic patients who gained weight had lower adiponectin levels and it was concluded that the decrease in adiponectin levels was the result of negative feedback inhibition as a consequence of increased fat mass [27]. It has also been reported that VPA inhibits adiponectin expression through the inhibition of histone deacetylases resulting in an increased gluconeogenesis process [28]. Despite similar BMIs and male/female ratios, adiponectin levels were significantly lower in the VPA group than the other groups in our study.

The IMT of the intracranial part of the carotid arteries is accepted as a measurable indicator of atherosclerosis. The

coronary, carotid, and femoral arteries have similar laminar flows. Carotid arteries are preferred in atherosclerosis assessment, as they are easily screened [29]. Carotid IMT measurement by ultrasound is a cheap, reliable, and repeatable method [30]. Previous studies have investigated the association of the use of AEDs and IMT values of the carotid arteries, but results are conflicting. Hamed et al. investigated CCA IMT measurements in epileptic patients using AEDs and drug-free patients. For the first time, they reported increased CCA IMT in both groups of epileptic patients regardless of drug use status. A greater increase in the CCA IMT was observed in the CBZ group. In the same study, an increase in vascular risk factors such as homocysteine, fibrinogen, malondialdehyde, and ox-LDL levels was shown together with a decrease in HDL and total antioxidant capacity. Considering these parameters, it was emphasized that epilepsy itself and/or AED therapy exposes the individual to atherosclerosis risk [3]. Tan et al. assessed 195 epileptic patients (60 of them receiving monotherapy) and 195 healthy participants and found higher CCA IMT values in the epileptic participants compared to the healthy controls. They found no difference between those taking VPA, liver enzyme inducer AEDs (phenytoin, phenobarbital, and carbamazepine), and polytherapy. The authors attributed the difference between the control group and patient group not to drug use but to the epilepsy itself and the oxidative stress arising from seizures. The same study noted higher CCA IMT levels in males and attributed that result to lifestyle factors [8]. On the other hand, a few studies have demonstrated no increase in CCA IMT [31-33]. Tokgoz et al. investigated changes in insulin, some adipocytokines, and carotid artery IMT, comparing pretreatment values and values obtained 6 and 12 months after the beginning of treatment [32]. In the review conducted by Lai et al., it was reported that AED usage was associated with CA IMT in patients with epilepsy, and especially among adult patients. In particular, CBZ and VPA may be related to a significant increase in CA IMT [34].

In this study, similar mean values of CCA IMT and ICA IMT were found among the patient and control groups. We reassessed the patient groups by developing two subgroups (duration of therapy ≤5 years and >5 years). There were no significant differences in terms of mean IMT, lp(a), ox-LDL, adiponectin, or TG levels, while patients using VPA for longer than 5 years had higher TC and LDL levels. In the CBZ subgroups, no significant differences were found between mean CCA IMT, ICA IMT, lp(a), ox-LDL, adiponectin, or TG levels.

This study has some potential limitations. The sample size is relatively small and may have resulted in limited statistical power. The cross-sectional design of the study is another limitation. Despite these limitations, our study is valuable for having taken advantage of testing atherosclerotic markers together with the lipid profile, ox-LDL, lp(a), adiponectin, and carotid artery IMT within a single work.

In conclusion, according to biochemical analysis and carotid IMT measurements, no significant result that could be interpreted as an increase in atherosclerosis risk was found regarding AED usage, except for high TC and LDL levels among patients using VPA for longer than 5 years. It is important to monitor lipid levels during the follow-up of patients with epilepsy, especially those patients who require long-term antiepileptic therapy and also older patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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